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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,558	03/14/2001	Michael M. Becker	GP068-05.CN3	3920

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/02/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,558	BECKER ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *422-463* is/are pending in the application.

4a) Of the above claim(s) *441-463* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *422-440* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 5 7,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *See Continuation Sheet* .

DETAILED ACTION

Election/Restriction

1. Applicant's election of 2'-O-methyl as the 2'-O-alkyl species in Paper No. 9, filed 10/1/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant's election with traverse of Group I, claims 422-440, in Paper No. 12, filed 1/22/03, is acknowledged. The traversal is on the ground(s) that (1) "the burden on the Examiner to search both groups of claims would not be significantly greater than the burden on the Examiner to search any one of the restriction groups. For example, to conduct a search of prior art relevant to the claims of Group II, the Examiner would necessarily have to search art which might disclose the compositions of the claims of Group I. If, during such search, the Examiner discovered prior art which disclosed the claimed compositions for uses other than the claimed use, it would be incumbent upon the Examiner to determine whether such prior art would suggest or motivate the claimed use. Thus, maintaining all pending claims in a single application should not add to the Examiner's search burden." ; (2) "In addition, the Examiner's contention that the oligonucleotides recited in the claims of Group I might be used as nucleic acid expression inhibitors is unsupported. While the Examiner is not required to document an alternative use example... Applicants submit that the Examiner's suggested alternative use is impracticable for a

couple of reasons. First, the claimed oligonucleotides include regions which are self-hybridizing under nucleic acid assay conditions, a feature which would interfere with their use as expression inhibitors... under physiological conditions. Second, the claimed oligonucleotides are capable of being detected when hybridized to a nucleic acid analyte under nucleic acid conditions. However, the Examiner has not explained how such detection would be achieved with antisense oligonucleotides unless such oligonucleotides were being used as detection probes. Therefore, Applicants submit that the burden has shifted to the Examiner to support the alleged alternative use or to establish another viable, alternative use. Absent such a showing, Applicants submit that the Examiner must withdraw the restriction requirement."

This is not found persuasive because the search burden weighted by the Examiner also included a consideration of the classification of the claimed inventions of Groups I and II. The invention of Group I is classified in class 536, subclasses 23.1, 24.31, 24.33 and 24.5. The invention of Group II is classified in class 435, subclass 6. Thus, the two groups are describing different classes of inventions, Group I is a product composition, and Group II is a method of use invention. Although applicant points out that the product compositions of Group I are useful in the methods of Group II, the composition is still able to be restricted from the method if the product can be used in another method than that claimed in group II. Applicant traverses the reasoning given that the oligonucleotides of Group I may be used as nucleic acid expression inhibitors such as antisense oligonucleotides as restated above. Applicant asserts that since there is a region in the oligonucleotides of Group I, that hybridizes to another region of the nucleic acid

oligonucleotide, that such compositions are not useful as antisense compositions. This is not validated since there are known uses in the art for making oligonucleotide compositions that have either hairpin stem loops at the end of the oligonucleotide for stability, or oligonucleotides having a region of complementary at the 5' and 3' ends, that form a loop structure in the oligonucleotide, but retain the function of detecting and binding a target nucleic acid for antisense oligonucleotide uses. See for example Azhayeva et al. page 4260, col. 1, lines 6-8, who taught oligonucleotides modified with 2'-O-methylribosides having hairpin hybridizing loops that retain the function of detecting and binding the target nucleic acid in the non-hairpin region of the oligonucleotide.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 441-463 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12, filed 1/22/03.

Claim Objections

4. Claim 422, line 1 is objected to for missing a preposition, "of", between "presence " and "a nucleic acid analyte".

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 422, 423, 425, 426, 429, 434, 435, 436, 437 and 440 are rejected under 35 U.S.C. 102(b) as being anticipated by Azhayeva et al. (*Nucleic Acids Research*, 1995, Vol. 23, No. 21, pp. 4255-4261).

Claim 422 is drawn to an oligonucleotide for determining the presence of a nucleic acid analyte in a sample comprising:

a first base region having at least one ribonucleotide modified to include a 2'-O-alkyl (elected species is a 2'-O-methyl) substitution to the ribofuranosyl moiety; and

a second base region, wherein the first and second base regions hybridize to each other under nucleic acid assay conditions to form a hybrid more stable than a hybrid formed between unmodified forms of the first and second base regions, and wherein the oligonucleotide forms a hybrid with the nucleic acid analyte but not with a non-targeted nucleic acid under nucleic acid assay conditions, such that the nucleic acid analyte can be detected. Claim 440 taught the

oligonucleotide of claim 422, wherein the 2'-O-alkyl substitution to the ribofuranyosyl moiety is a 2'-O-methyl substitution.

Azhayeva et al. taught oligonucleotides modified with 2'-O-methylribosides having loops (hairpin hybridizing) structures where the oligonucleotides having the 2'-O-methyl substitution was stable, and the unmodified (2'-deoxyribosides) was not stable. (See page 4260, col. 1, lines 6-8) Since the structure of the claimed oligonucleotide was taught by Azhayeva et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Azhayeva et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Thus, Azhayeva et al. anticipated all of the claimed limitations.

Claim 423 states the oligonucleotide of claim 422, wherein the first base region includes a cluster of at least about 4 ribonucleotides modified to include a 2'-O-alkyl (2'-O-methyl) substitution to the ribofuranosyl moiety.

The oligonucleotides taught by Azhayeva et al. were 2'-O-methyl substituted at every base. Thus their oligonucleotides had at least 4 such modifications (since their oligonucleotides were longer than four bases). See page 4255, col. 2.

Claim 425 states the oligonucleotide of claim 422, wherein each nucleotide of the first base region is a ribonucleotide modified to include a 2'-O-alkyl (2'-O-methyl) substitution to the ribofuranosyl moiety.

The oligonucleotides taught by Azhayeva et al. were 2'-O-methyl substituted at every base. See page 4255, col. 2.

Claim 426 states the oligonucleotide of claim 422, wherein each nucleotide of the oligonucleotide is a ribonucleotide modified to include a 2'-O-alkyl (2'-O-methyl) substitution to the ribofuranosyl moiety.

The oligonucleotides taught by Azhayeva et al. were 2'-O-methyl substituted at every base. See page 4255, col. 2.

Claim 429 states the oligonucleotide of claim 422, wherein the oligonucleotide is up to about 100 bases in length.

Figure 1 (page 4256) of Azhayeva et al. shows the oligonucleotides they used. All of their oligonucleotides were under 100 bases.

Claim 434 states the oligonucleotide of claim 422, wherein the oligonucleotide is a hybridization assay probe which forms a detectable hybrid with the nucleic acid analyte.

Azhayeva et al. taught the design of their oligonucleotides for binding to a single-stranded complementary DNA sequence (page 4255, col. 2, lines 1-2).

Claim 435 states the oligonucleotide of claim 422, wherein the oligonucleotide is an amplification primer for use in an amplification procedure.

Azhayeva et al. taught on page 4257, that the oligonucleotides were used in amplification reactions with Sequenase enzyme.

Claim 436 states the oligonucleotide of claim 435, wherein the amplification procedure is a polymerase chain reaction method of amplification.

On page 4259, Azhayeva et al. taught that Klenow polymerase was also used to amplify the modified primers at an elevated temperature 55C.

Claim 437 states the oligonucleotide of claim 435, wherein the amplification procedure is a transcription-based method of amplification.

Both the Sequenase and the Klenow methods taught by Azhayeva et al. were transcription based amplification reactions.

7. Claims 422, 424, 426, 429 and 440 are rejected under 35 U.S.C. 102(b) as being anticipated by Lubini et al. (*Current Biology* Vol. 1, No. 1, 1994, pp. 39-45).

Claim 422 is drawn to an oligonucleotide for determining the presence of a nucleic acid analyte in a sample comprising:

a first base region having at least one ribonucleotide modified to include a 2'-O-alkyl (elected species is a 2'-O-methyl) substitution to the ribofuranosyl moiety; and

a second base region, wherein the first and second base regions hybridize to each other under nucleic acid assay conditions to form a hybrid more stable than a hybrid formed between

unmodified forms of the first and second base regions, and wherein the oligonucleotide forms a hybrid with the nucleic acid analyte but not with a non-targeted nucleic acid under nucleic acid assay conditions, such that the nucleic acid analyte can be detected. Claim 440 taught the oligonucleotide of claim 422, wherein the 2'-O-alkyl substitution to the ribofuranyosyl moiety is a 2'-O-methyl substitution.

Lubini et al. taught in Figure 1, page 40, the sequence of a self-complementary 2'-O-methylated RNA-DNA chimera. They further taught that the 2'-O-methyl modification is more stable that the unmodified sequence (abstract). Since the structure of the claimed oligonucleotide was taught by Lubini et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Lubini et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Thus, Lubini et al. anticipated all of the claimed limitations.

Claim 424 states the oligonucleotide of claim 422, wherein the first base region includes at least one nucleotide which is not a ribonucleotide modified to include a 2'-O-alkyl substitution to the ribofuranosyl moiety.

Lubini et al. taught in Figure 1, page 40, that the sequence of the self-complementary oligonucleotide contains some 2'-O-methylated nucleotides (in italics) and the DNA residues are not methylated (in bold).

Claim 426 states the oligonucleotide of claim 422, wherein each nucleotide of the oligonucleotide is a ribonucleotide modified to include a 2'-O-alkyl (2'-O-methyl) substitution to the ribofuranosyl moiety.

The nucleic acid in Figure 1, page 40, shows that only the RNAs (having a ribofuranosyl moiety) are the nucleic acids that are methylated.

Claim 429 states the oligonucleotide of claim 422, wherein the oligonucleotide is up to about 100 bases in length.

The nucleic acid in Figure 1, page 40, is less than 100 nucleic acid bases.

Claim 434 states the oligonucleotide of claim 422, wherein the oligonucleotide is a hybridization assay probe which forms a detectable hybrid with the nucleic acid analyte.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 422, 423, 427, 428, 430, 431, 438 and 439 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azhayeva et al. (*Nucleic Acids Research*, 1995, Vol. 23, No. 21, pp. 4255-4261) or Lubini et al. (*Current Biology* Vol. 1, No. 1, 1994, pp. 39-45) cited above in the 35 U.S.C. 102 rejection over claims 422 and 423, either in view of Réfrégiers et al. (*Journal of Biomolecular Structure & Dynamics*, Vol. 14, No. 3, 1996, pp. 365-371).

Claim 422 is drawn to an oligonucleotide for determining the presence of a nucleic acid analyte in a sample comprising:

a first base region having at least one ribonucleotide modified to include a 2'-O-alkyl (elected species is a 2'-O-methyl) substitution to the ribofuranosyl moiety; and

a second base region, wherein the first and second base regions hybridize to each other under nucleic acid assay conditions to form a hybrid more stable than a hybrid formed between unmodified forms of the first and second base regions, and wherein the oligonucleotide forms a hybrid with the nucleic acid analyte but not with a non-targeted nucleic acid under nucleic acid assay conditions, such that the nucleic acid analyte can be detected. Claim 440 taught that the oligonucleotide of claim 422, wherein the 2'-O-alkyl substitution to the ribofuranyosyl moiety is a 2'-O-methyl substitution.

Claim 423 states the oligonucleotide of claim 422, wherein the first base region includes a cluster of at least about 4 ribonucleotides modified to include a 2'-O-alkyl (2'-O-methyl) substitution to the ribofuranosyl moiety.

Claim 427 states the oligonucleotide of claim 422, wherein the oligonucleotide includes a conjugate molecule.

Claim 428 states the oligonucleotide of claim 423, wherein the oligonucleotide includes a conjugate molecule joined to the oligonucleotide at a site located within the cluster of the first base region.

Claim 430 states the oligonucleotide of claim 422, wherein the oligonucleotide includes a reporter group.

Claim 431 states the oligonucleotide of claim 430, wherein the reporter group comprises a fluorescent molecule.

Claim 438 states the oligonucleotide of claim 422, wherein the oligonucleotide is a target capture oligonucleotide.

Claim 439 states the oligonucleotide of claim 438, wherein the target capture oligonucleotide is immobilized by a solid support.

Azhayeva et al. taught oligonucleotides modified with 2'-O-methylribosides having loops (hairpin hybridizing) structures where the oligonucleotides having the 2'-O-methyl substitution was stable, and the unmodified (2'-deoxyribosides) was not stable. (See page 4260, col. 1, lines 6-8) The oligonucleotides taught by Azhayeva et al. were 2'-O-methyl substituted at every base. Thus their oligonucleotides had at least 4 such modifications (since their oligonucleotides were longer than four bases). See page 4255, col. 2. Since the structure of the claimed

oligonucleotide was taught by Azhayeva et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Azhayeva et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Thus, Azhayeva et al. anticipated all of the claimed limitations of claim 422. They did not specifically teach conjugates of the oligonucleotides such as with fluorescent reporters or immobilization of the oligonucleotides on a solid support.

Lubini et al. taught in Figure 1, page 40, the sequence of a self-complementary 2'-O-methylated RNA-DNA chimera. They further taught that the 2'-O-methyl modification is more stable that the unmodified sequence (abstract). Since the structure of the claimed oligonucleotide was taught by Lubini et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Lubini et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Thus, Lubini et al. anticipated all of the claimed limitations of claim 422. They did not specifically teach conjugates of the

oligonucleotides such as with fluorescent reporters or immobilization of the oligonucleotides on a solid support.

Réfrégiers et al. taught antisense oligonucleotides labeled on their 5' side by tetramethylrhodamine and on their 3' side by fluorescein (see abstract and page 367, first paragraph). Their oligonucleotides did not contain the 2'-O-methyl modification for stability of the oligonucleotide, but they did teach the importance and necessity of stability of oligonucleotides on page 365, the introduction section. They taught use of their oligonucleotides immobilized on a solid support in figure 1 on page 366 and detection of the sample(s) with a confocal laser for detection of the rhodamine and fluorescein fluorescence. The "microsample" immobilized on the slide contains the labeled oligonucleotides and is used in the detection of the oligonucleotides by confocal microscopy.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a conjugate of the oligonucleotides taught by Azhayeva et al. or Lubini et al. with a fluorescent reporter such as Réfrégiers et al. for detection of the oligonucleotide as taught by Réfrégiers et al. on a solid support.

One of ordinary skill in the art would have been motivated to stabilize short oligonucleotides with 2'O-methyl as taught in Azhayeva et al. and Lubini et al. above and to further add fluorescent detection groups as taught by Réfrégiers et al. for use in methods of detection of nucleic acid sequences and immobilization on a solid support since Réfrégiers et al. taught both the motivation to optimize the stability of oligonucleotides (page 365, the

introduction section) as well as use fluorescent side groups and immobilization on a solid support in a detection method with oligonucleotides. One of ordinary skill in the art would have been motivated to immobilize a detection oligonucleotide (such as those taught by Azhayeva et al. and Lubini et al.) since Réfrégiers et al. taught the benefits of immobilization of detection probe oligonucleotides having a fluorescent side group on a slide for detection and measurement of the fluorescence by a confocal microscrope.

10. Claims 422, 432 and 433 are rejected under 35 U.S.C. 103(a) as being unpatentable over Azhayeva et al. (*Nucleic Acids Research*, 1995, Vol. 23, No. 21, pp. 4255-4261) or Lubini et al. (*Current Biology* Vol. 1, No. 1, 1994, pp. 39-45) cited above in the 35 U.S.C. 102 rejection over claims 422 and 423, either in view of Barry et al. (U.S. Patent 5,574,145) and Roseau et al. (U.S. Patent 5,536,638).

Claim 422 is drawn to an oligonucleotide for determining the presence of a nucleic acid analyte in a sample comprising:

a first base region having at least one ribonucleotide modified to include a 2'-O-alkyl (elected species is a 2'-O-methyl) substitution to the ribofuranosyl moiety; and

a second base region, wherein the first and second base regions hybridize to each other under nucleic acid assay conditions to form a hybrid more stable than a hybrid formed between unmodified forms of the first and second base regions, and wherein the oligonucleotide forms a hybrid with the nucleic acid analyte but not with a non-targeted nucleic acid under nucleic acid

assay conditions, such that the nucleic acid analyte can be detected. Claim 440 taught that the oligonucleotide of claim 422, wherein the 2'-O-alkyl substitution to the ribofuranyosyl moiety is a 2'-O-methyl substitution.

Claim 432 is drawn to the oligonucleotide of claim 422, wherein the nucleic acid analyte comprises RNA.

Claim 433 is drawn to the oligonucleotide of claim 432, wherein the nucleic acid analyte comprises ribosomal RNA.

Azhayeva et al. taught oligonucleotides modified with 2'-O-methylribosides having loops (hairpin hybridizing) structures where the oligonucleotides having the 2'-O-methyl substitution was stable, and the unmodified (2'-deoxyribosides) was not stable. (See page 4260, col. 1, lines 6-8) The oligonucleotides taught by Azhayeva et al. were 2'-O-methyl substituted at every base. Thus their oligonucleotides had at least 4 such modifications (since their oligonucleotides were longer than four bases). See page 4255, col. 2. Since the structure of the claimed oligonucleotide was taught by Azhayeva et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Azhayeva et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been

established." Thus, Azhayeva et al. anticipated all of the claimed limitations of claims 422 or 423. They did not specifically teach that the analyte detected comprised RNA such as ribosomal RNA.

Lubini et al. taught in Figure 1, page 40, the sequence of a self-complementary 2'-O-methylated RNA-DNA chimera. They further taught that the 2'-O-methyl modification is more stable that the unmodified sequence (abstract). Since the structure of the claimed oligonucleotide was taught by Lubini et al., the claimed functions "for determining the presence of a nucleic acid analyte in a sample" and "such that the nucleic acid analyte can be detected" would have been an inherent property of the oligonucleotide taught by Lubini et al. Note MPEP 2112.01 that states "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Thus, Lubini et al. anticipated all of the claimed limitations of claims 422 and 423. They did not specifically teach that the analyte detected comprised RNA such as ribosomal RNA.

Barry et al. (U.S. Patent 5,574,145) is relied upon to have taught the motivation in the prior art for probing for ribosomal RNA, rRNA, gene sequences: "[t]he choice of a target sequence for a probe currently involves a) the identification of an area of sufficient interspecies diversity or variation that will allow for the provision of a specific probe and b) a target which is preferably present in the organism in a high number of copies. The rRNA gene products (16S and 23S) appear to fulfil both of these criteria and as such have been the target for many studies

and, indeed, DNA probe kits directed to those regions are available commercially for some organisms. Most comparisons to date have been between the rRNA genes from different genera and these have highlighted a pattern of variable regions within the gene flanked by adjacent more conserved regions." (Col. 2, lines 22-35; see also col. 9, line55, through col. 10, line26) They did not specifically teach use of probes having the 2'-O-methyl modification although they did teach the necessity for stability of the probe depending on hybridization conditions and that the probe may be "optimized" for stability (see col. 1, lines 50-64, especially line 60)

Roseau et al. (U.S. Patent 5,536,638) also taught: "nucleic acid probes derived from the spacer region between the ribosomal ribonucleic acid (rRNA) gene, particularly between the 16S and 23S rRNA genes, to be used for the specific detection of non-viral organisms in a biological sample by a hybridization procedure.... These nucleic acid probes can, for instance, be total genomic deoxyribonucleic acid (DNA), plasmids, ribo-probes or synthetic oligonucleotides and these probes may target the genomic DNA or messenger or stable RNA species present in biological samples." (Col. 1, lines 16-29) they further taught in col. 14, lines 8-25) that "[i]t is also understood that the word "nucleotide" as used herein refers indistinctly to ribonucleotides and deoxyribonucleotides and modified nucleotides such as inosine unless otherwise specified. The expression "nucleotides" also encompasses those which further comprise modification groups, e.g. chemical modification groups which do not affect their hybridization capabilities fundamentally. Such modification groups aim, for instance, at facilitating their coupling, either directly or indirectly, with suitable markers or labels for the subsequent detection of the probes so

marked or labeled particularly in their hybridization products with the relevant RNA or DNA strand...." Thus, they taught motivation for modification of the probes albeit not specifically the 2'-O-methyl modification.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the 2'-O-methyl modified oligonucleotides of Azhayeva and Lubin et al. for use in targeting a ribosomal RNA, rRNA, sequence for the reasons taught by Barry et al. and Roseau et al. since they taught that oligonucleotides were used for detecting rRNA and that such oligonucleotides optionally contained nucleic acid modifications encompassing the 2'-O-methyl modification taught by Azhayeva et al. and Lubini et al.

One of ordinary skill in the art would have been motivated to design oligonucleotide probes to rRNA for the detection of rRNA as taught by Barry et al. and Roseau et al. and where said oligonucleotide probes had optimized modifications such as those taught by Azhayeva et al. and Lubini et al. having oligonucleotide 2'O-methyl modifications for improved nucleic acid stability. Specifically, since Barry et al. and Roseau et al. both taught the motivation for probing for rRNA gene sequences as summarized above, and since Roseau et al. specifically taught the motivation to use oligonucleotides having modifications for facilitating their use as probes to the rRNA, one of skill in the art would have been motivated to probe for rRNA as a target (Barry et al. and Roseau et al.) as well as to have made modifications to the rRNA probes such as those taught by Azhayeva et al. and Lubini et al. for improved probe stability.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Inquiries relating to the status of this application may also be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

M. M. Schmidt
May 28, 2003